UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/506,978 | 02/18/2000 | Francois Spertini | 18519-001 | 9105 |

30623 7590 12/19/2003

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

| EXAMINER | |
|---|---|
| HUYNH, PHUONG N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

S-M

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/506,978 | SPERTINI, FRANCOIS | |
| | Examiner | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *28,29 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-29 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**DETAILED ACTION**

1. Claims 28-29 and 36 are pending.

2. In view of the amendment filed 9/9/03, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 28-29 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of modulating an immune response, said method comprising administering a substantially pure polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 to a subject in need thereof in an amount sufficient to inhibit T cell response by the subject against said polypeptide, the said method further comprising administering a second bee venom polypeptide selected from the group consisting of the ones recited in claim 30, **does not** reasonably provide enablement for (1) a method of modulating an immune response to bee venom, said method comprising administering a substantially pure bee venom polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 to a subject in need thereof in an amount sufficient to inhibit *any* "immune response" by the subject against said bee venom, (2) The said method further comprising administering a second bee venom polypeptide to said subject, wherein the second bee venom polypeptide is selected from the group consisting of phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase, (3) The said method further comprising administering one or more additional bee venom polypeptide to said subject, wherein one or more additional bee venom polypeptide to said subject, wherein the second bee venom polypeptide is selected from the group consisting of phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase for inhibiting *any* immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only 4 full-length polypeptides of SEQ ID NOS: 1-4 for a method of inhibiting T cell response in a subject who is sensitive to a protein allergen from bee venom (see page 19). The specification discloses Api m 6 peptide of SEQ ID NO: 1 overlaps by at least 3, between 5 and 10 amino acids (See page 9 at lines 9-23 of specification). The specification further discloses fragments of SEQ ID NO: 1-4 wherein the fragment has Api m6 protein activities and can be, e.g., 6-72, 20-90, 30-70, or 40-60 amino acids in length on page 11 at lines 19-22.

The specification does not teach how to use *any* bee venom polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 either alone or in combination of any one or more bee venom polypeptide such as phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase for inhibiting *any* immune response. The specification on page 3 discloses that the method includes administering an Api m6 polypeptide of SEQ ID NO: 1 to a subject to **inhibit** an immune reaction such as T-cell response or to diminish allergic response of a mammal (see page 19, at line 17) upon exposure to said polypeptide. There is insufficient guidance and working examples demonstrating that any combination of bee venom polypeptide such as phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase with bee venom polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 would result in inhibiting any immune response. The term "immune response" encompasses B cell, T cell response, etc. There is insufficient guidance as to which combination and subcombination of bee venom polypeptides would be useful for modulating an immune response such as inhibiting *any* immune response. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities.

Because of the lack of sufficient guidance and predictability in determining which combination and subcombination would lead to modulate any immune response such as inhibiting any immune response was not well understood and was not predictable (e.g. see Ngo et al., in The

Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.), it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the claimed invention.

Attwood *et al* (of record) teach that "It is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tell us functions)".

Fasler *et al.* (of record) teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 either with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al.* (of record) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al.* (of record) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the lack of guidance and the lack of working examples, the breadth of the claims that fail to recite any structural or functional limitations and the unpredictability of the art, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicant's arguments filed 9/9/03 have been fully considered but are not found persuasive.

Applicant's position is that (1) claims 30, 44-49 have been canceled and claims 28, 29 and 36 have been amended.

However, Claim 28 still recites inhibiting any immune response. The specification on page 3 discloses that the method includes administering an Api m6 polypeptide of SEQ ID NO: 1 to a subject to **inhibit** an immune reaction such as T-cell response or to diminish allergic response of a mammal (see page 19, at line 17) upon exposure to said polypeptide. There is insufficient guidance and working examples demonstrating that any combination of bee venom polypeptide such as phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase with bee venom polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 would result in inhibiting any immune response.

5. Claims 28-29 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) (1) a method of modulating an immune response to bee venom, said method comprising administering a substantially pure bee venom polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 to a subject in need thereof in an amount sufficient to inhibit *any* "immune response" by the subject against said bee venom, (2) The said method further comprising administering a second bee venom polypeptide to said subject, wherein the second bee venom polypeptide is selected from the group consisting of phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase, (3) The said method further comprising administering one or more additional

bee venom polypeptide to said subject, wherein one or more additional bee venom polypeptide to said subject, wherein the second bee venom polypeptide is selected from the group consisting of phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase for inhibiting *any* immune response.

The specification discloses only 4 full-length polypeptides of SEQ ID NOS: 1-4 for a method of inhibiting T cell response in a subject who is sensitive to a protein allergen from bee venom (see page 19). The specification discloses Api m 6 peptide of SEQ ID NO: 1 overlaps by at least 3, between 5 and 10 amino acids (See page 9 at lines 9-23 of specification). The specification further discloses fragments of SEQ ID NO: 1-4 wherein the fragment has Api m6 protein activities and can be, e.g., 6-72, 20-90, 30-70, or 40-60 amino acids in length on page 11 at lines 19-22. The specification discloses only 4 full-length polypeptides of SEQ ID NOS: 1-4 for a method of inhibiting T cell response in a subject who is sensitive to a protein allergen from bee venom (see page 19).

Other than inhibiting T cell response with the specific bee venom polypeptide of SEQ ID NO: 1 mentioned above, there is insufficient written description about the other immune response using the claimed polypeptide of SEQ ID NO: 1, much less the about the combination of polypeptide of SEQ ID NO: 1 with one or more additional bee venom polypeptide selected from the group consisting of phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase.

Given the lack of a written description of *any* additional representative species of combination of bee venom polypeptide as encompassed by the claimed method of inhibiting any immune response, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments filed 9/9/03 have been fully considered but are not found persuasive.

Applicant's position is that (1) claims 30, 44-49 have been canceled and claims 28, 29 and 36 have been amended.

However, Claim 28 still recites inhibiting any immune response. The specification on page 3 discloses that the method includes administering an Api m6 polypeptide of SEQ ID NO: 1 to a subject to inhibit T-cell response or to diminish allergic response of a mammal (see page 19, at line 17) upon exposure to said polypeptide. There is inadequate written description about the combination of bee venom polypeptide such as phospholipase A2, hyaluronidase, allergen C, mellitin, minimine and acid phosphatase with bee venom polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 would result in inhibiting *any* immune response.

6. Claims 28-29 and 36 are free of prior art.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located

in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
December 15, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600